IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of)
Yvin et al)
Serial No. : 10/698,034) Art Unit: 1642
Filed: October 30, 2003)Examiner:Fetterolf, Brandon J.

For : THERAPEUTICAL COMBINATION AGAINST CANCER.

DECLARATION UNDER RULE 132

To Honorable Commissioner of Patents and Trademarks
Washington, D.C.
Sir :

I, Vaclav VETVICKA, 3620 Brooklollow Drive, Louisville, KY 40220, United States of America, do solemnly declare :

THAT I have been working with the firm GOËMAR since 1999 by virtue of a research agreement executed on 2000.

THAT I am a named inventor of the present patent application n° 10/698,034 and that I am fully familiar therewith ;

THAT I have read and understood the Office Action of August 25, 2004 in connection with the present patent application ;

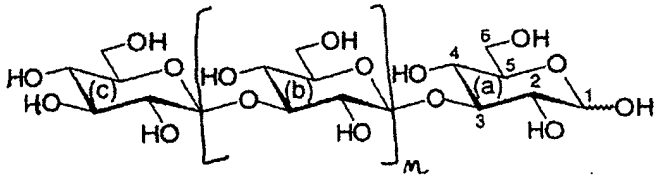
THAT, the experiments described in the attached test report were carried out under my supervision;

THAT, the administration of either Laminaritetraose or Laminaripentaose allows a decrease of the weight of the tumor,

- THAT, the administration of either Laminaritetraose or Laminaripentaose and Herceptin allows a decrease of

the weight of the tumor which is far higher than the mean value obtained when administering Laminaritetraose or Laminaripentaose alone,

- THAT, monoclonal antibody in combination with Laminaritetraose or Laminaripentaose can effectively be used for treating cancer,
- That, accordingly, the oligo-β-(1,3)-glucans of formula (1)



in which n=1 to 10,
in combination with a monoclonal antibody are effectively efficient in the treatment of cancer.

I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18, of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11-18-2004

Vaclav Vetvicka

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TEST REPORT

Athymic female nude mice *(nu/nu)* between 4 and 6 weeks of age weighing approximately 20g were obtained from Jackson Laboratories, USA. BT-474 human breast carcinoma cell line, obtained from the American Type Culture Collection (ATCC), in 0.1ml PBS were injected into the mammary pats of each mouse. All of the groups contained 6 mice. All of the animals were ear-tagged and followed individually throughout the experiment.

When tumor diameter reached 0.7 to 0.9 mm, usually 14 days after tumor cell injection, the treatment started.

The mice were administered daily for two weeks as follows:

Group 1: (control) sterile PBS, 5 times a day

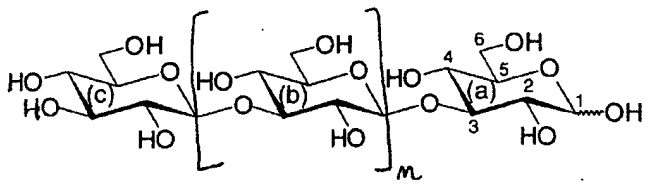
Group 2: Laminaritetraose(ip) 100µg/mouse,

Group 3: Laminaritetraose(ip) 100µg/mouse plus Herceptin(iv) 0.5mg/kg,

Group 4: Laminaripentaose (ip) 100µg/mouse,

Group 5: Laminaripentaose (ip) 100µg/mouse plus Herceptin (iv) 0.5mg/kg.

Laminaritetraose and Laminaripentaose are oligo-β-(1,3)-glucans of formula



wherein n=2 for Laminaritetraose, which is also called β-D-glucopyranosyl-(1→3)- β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranose, and wherein n=3 for Laminaripentaose which is also called the β-D-glucopyranosyl-(1→3)- β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranose.

Laminaritetraose and Laminaripentaose were synthesized by de-protection and purification of the compounds prepared according to the process disclosed in WO01/57053 in the name of the Assignee. Methods of de-protection and purification usable are described with reference to laminaribiose in FR2777281.

Mice were weighed sacrified two weeks after the beginning of the treatment; tumors were removed, trimmed of surrounding tissue and weighed.

The results which are expressed as mean value in mg are represented in Figure 1. On said Figure, the mean weight of the tumor for each group of mice is indicated on the ordinate as mg.

Those results show that:

- the administration of either Laminaritetraose or Laminaripentaose allows a decrease of the weight of the tumor;
- the administration of either Laminaritetraose or Laminaripentaose and Herceptin allows a decrease of the weight of the tumor which is far higher than the mean value

obtained when administering Laminaritetraose or Laminaripentaose alone.

Corresponding Figure 1 is presented in the Appendix (herewith attached).